Cardiovascular Complications of ADT: Reviewing Pre-clincal and Clinical Data and Introducing the RADICAL-PC Trial

Jehonathan H. Pinthus MD, Ph.D.
Associate professor
Department of Surgery-Urology
McMaster University

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Faculty/presenter disclosure

• Faculty: Jehonathan H. Pinthus MD, Ph.D.

• Relationships with commercial interests:
  – Grants/Research Support: Ferring Inc.
  – Consulting Fees: Ferring Inc.
Stable coronary artery disease

Atherosclerosis timeline

- Foam cells
- Fatty streak
- Intermediate lesion
- Atheroma
- Fibrous plaque

Endothelial dysfunction

- From first decade: Growth mainly by lipid accumulation
- From third decade: Smooth muscle and collagen
- From fourth decade:

Adapted from Pepine CJ. Am J Cardiol
Acute/ unstable coronary artery disease

Atherosclerosis timeline

From first decade
- Growth mainly by lipid accumulation

From third decade
- Smooth muscle and collagen

From fourth decade
- Thrombosis, hematoma

Adapted from Pepine CJ. Am J Cardiol. 1998;82(suppl 104).
Epidemiology of CVD in PC patients

- patients are deemed to be high risk if they have a global risk estimate for hard CVD events of ≥2% per year

Prostate cancer is a diagnosis that is associated with a high subsequent risk of cardiovascular disease

Comprehensive prospective metabolic, anthropometric, nutritional and physical profiling of prostate cancer patients

**Fasting Insulin (μIU/mL)**

- **Gleason 6 (3+3)**
- **Gleason 7 (3+4)**
- **Gleason 7+ (4+3)**

**Fasting C-Peptide (ng/mL)**

- **Whole Cohort**
- **No Cancer**
- **Gleason 6 (3+3)**
- **Gleason 7 (3+4)**
- **Gleason 7+ (4+3)**

**Adiponectin (pg/mL)**

**Leptin: Adiponectin Ratio (AU)**

* Di Sebastiano et al in preparation
PC patients are at high risk of CVD

- Risk of MI, stroke, or CV death in PC patients >2% per year\(^1,2\)
- Risk of MI, stroke, or CV death in PC patients on ADT >4% per year\(^1,2\)
- CVD risk considered high if global risk estimate for hard CVD events of ≥2% per year\(^3\)

US Veterans with Locoregional PC

Incidence of CVD (% per year)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Coronary heart disease</th>
<th>MI</th>
<th>Sudden Cardiac Death</th>
<th>Stroke</th>
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<tbody>
<tr>
<td>No ADT</td>
<td>8.1</td>
<td>0.73</td>
<td>1.15</td>
<td>1.08</td>
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<td>GnRH agonist</td>
<td>14.4</td>
<td>1.28</td>
<td>2.16</td>
<td>1.85</td>
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</table>

Novel ADT agents

### Table A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>new HA Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
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<tr>
<td>AFFIRM</td>
<td>49</td>
<td>30</td>
<td>800</td>
<td>12.9%</td>
<td>0.81</td>
<td>[0.53, 1.26]</td>
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<tr>
<td>COU-AA-301</td>
<td>126</td>
<td>46</td>
<td>791</td>
<td>18.9%</td>
<td>1.36</td>
<td>[1.00, 1.87]</td>
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<tr>
<td>COU-AA-302</td>
<td>126</td>
<td>96</td>
<td>542</td>
<td>23.9%</td>
<td>1.31</td>
<td>[1.03, 1.66]</td>
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<tr>
<td>ELM-PC 4</td>
<td>172</td>
<td>100</td>
<td>784</td>
<td>24.8%</td>
<td>1.69</td>
<td>[1.35, 2.12]</td>
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<tr>
<td>PREVAIL</td>
<td>88</td>
<td>66</td>
<td>871</td>
<td>19.5%</td>
<td>1.29</td>
<td>[0.95, 1.75]</td>
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</table>

**Total (95% CI)**

| Total | 3788 | 2947 |

**Total events**

<table>
<thead>
<tr>
<th>AFFIRM</th>
<th>561</th>
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</thead>
</table>

**Heterogeneity**

- $\tau^2 = 0.03$
- $\chi^2 = 9.01$, df = 4 (P = 0.06)
- $I^2 = 56\%$

**Test for overall effect**

- $Z = 2.77$ (P = 0.006)

### Table B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>new HA Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>M-H, Random, 95% CI</th>
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<td>COU-AA-302</td>
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<td>23</td>
<td>542</td>
<td>23.8%</td>
<td>1.95</td>
<td>[1.20, 3.18]</td>
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<td>ELM-PC 4</td>
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<td>46</td>
<td>784</td>
<td>27.6%</td>
<td>1.17</td>
<td>[0.80, 1.72]</td>
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<td>PREVAIL</td>
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<td>18</td>
<td>871</td>
<td>20.2%</td>
<td>1.29</td>
<td>[0.71, 2.36]</td>
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</table>

**Total (95% CI)**

| Total | 3788 | 2947 |

**Total events**

| AFFIRM | 172  |

**Heterogeneity**

- $\tau^2 = 0.12$
- $\chi^2 = 9.58$, df = 4 (P = 0.05)
- $I^2 = 58\%$

**Test for overall effect**

- $Z = 1.46$ (P = 0.15)

*Jacovelli R et al European Journal of Cancer 2015*
Randomized Trials of ADT vs. Control: CV Mortality

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<thead>
<tr>
<th>Source</th>
<th>ADT No./Total</th>
<th>Control No./Total</th>
<th>Relative Risk (95% CI)</th>
<th>Favors ADT</th>
<th>Favors Control</th>
<th>P Value</th>
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<td>D’Amico et al,3 2008 (DFCI 95-096)</td>
<td>13/102</td>
<td>13/104</td>
<td>1.02 (0.50-2.09)</td>
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<td>Messing et al,12 2006 (ECOG/EST 3886)</td>
<td>3/47</td>
<td>1/51</td>
<td>3.26 (0.35-30.2)</td>
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<td>Bolla et al,13 2010 (EORTC 22863)</td>
<td>22/207</td>
<td>17/208</td>
<td>1.30 (0.71-2.38)</td>
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<td>Schröder et al,14 2009 (EORTC 30846)</td>
<td>10/119</td>
<td>10/115</td>
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<td>Studer et al,15 2006 (EORTC 30891)</td>
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<td>0.91 (0.70-1.18)</td>
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<td>Efstathiou et al,8 2009 (RTOG 85-31)</td>
<td>52/477</td>
<td>65/468</td>
<td>0.78 (0.56-1.10)</td>
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<td>Roach et al,9 2008 (RTOG 86-10)</td>
<td>31/224</td>
<td>26/232</td>
<td>1.23 (0.76-2.01)</td>
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<td>.40</td>
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<td>Denham et al,16 2011 (TROG 96.01)</td>
<td>36/532</td>
<td>23/270</td>
<td>0.79 (0.48-1.31)</td>
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<tr>
<td>Overall</td>
<td>255/2200</td>
<td>252/1941</td>
<td>0.93 (0.79-1.10)</td>
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<td>.41</td>
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</table>

Test for heterogeneity: $Q=5.12; P=.64; \hat{\tau}^2=0\%$
Take home massage #1

- CVS disease and its risk factors are common among PC patients.
- Higher risk in more aggressive disease?
- Observational data suggest that the risk significantly increase with all forms of ADT.
How might ADT accelerate CVD?

CVS (atherosclerosis) risk factors

- Dysglycemia
- Central adiposity
- Dyslipidemia
- Changes in lifestyle

Testosterone
FSH
GnRH
Est

Plaque vulnerability

Cardiovascular event

Reproduced from Falk L et al. Circulation 2002
Reproduced from Falk L et al. Circulation 2002
FSH is a trophic hormone

Males: stimulates seminiferous to produce sperm
Females: stimulates granulosa cells in the ovarian follicle
Common: steroidogenesis, energy and metabolism, protein synthesis, cell division, growth and differentiation, calcium intake

1. Data source: www.biogps.org
What happens to FSH with different modes of ADT?

• Orchiectomy: ↑
• GNRH analogues: ↓ (~50%)/escape?
• GNRH antagonists: ↓ (90%)
FSH may facilitate pro-atherogenic risk factors and effect the development of CVS events

- Development of dysfunctional fat tissue
- Effects on atherosclerotic plaque stability
Lessons learnt from menopause

- Menopause occurs at an average age of 51 (range 44–59)
- Ovarian function declines before menopause (4–5 years) - reduced inhibin levels and increased FSH levels; Estrogen and progesterone levels maintained
- After the menopause, FSH levels rise 10-15-fold, with low estradiol

20 year old (young)  | 50 year old (middle age)  | >70 year old (old age)

- Subcutaneous depot
- Visceral depot
- Ectopic tissue depot (bone marrow, muscle and liver)

Burger HG. Eur J Endocrinol 1994;130:38–42
Correlation between FSH levels and BMI in aging males and females

Males (n=414, age 61-65 yrs)

Females (n=499, age 51-55 yrs)

\[ \Delta \text{BMI} = \text{BMI (present)} - \text{BMI (age 35-45)} \]

\[ \Delta \text{BMI} = \text{BMI (post-menapausal)} - \text{BMI (pre-menapausal)} \]

FSH induces adipogenesis in vitro

Liu et al 2015

Zaereba et al 2015
GnRH antagonist associates with less adiposity and reduced characteristics of metabolic syndrome and atherosclerosis compared with orchiectomy and GnRH agonist in a preclinical mouse model

Sarah N. Hopmans, M.Sc. a,1, Wilhelmina C.M. Duivenvoorden, Ph.D. a,1, Geoff H. Werstuck, Ph.D. b,c, Laurence Klotz, M.D. d, Jehonathan H. Pinthus, M.D., Ph.D. a,*

Control
(sham surgery + vehicle)

Bilateral orchiectomy
(+ vehicle)

GnRH-agonist, leuprolide
(+ sham surgery)

GnRH-antagonist, degarelix
(+ sham surgery)
ADT induced obesity

N = 6 per group

ADT induced glucose intolerance

Fig. 7. (A) Blood glucose and (B) glucose tolerance measured after overnight fasting of LDLR−/− mice receiving different modes of ADT (n = 9–13/group) at 14 weeks. Data shown represent mean ± SEM. 

aP < 0.05 vs. control; bP < 0.05 vs. orchietomy; cP < 0.05 vs. leuprolide.

The effect of ADT on the development of atherosclerotic plaques in mice

• Mice are relatively atheroprotected (High HDL).

• In-order to induce atherosclerosis one needs to manipulate lipoproteins (Apo E-/-, LDLr-/-) and stimulate with high fat diet.

**ADT an atheroogenic (enough) stimulus**
ADT induced (de-novo) atherosclerosis

Fig. 8. (A) Aortic atherosclerotic plaque area in LDLR−/− mice receiving different modes of ADT (n = 9–13/group) at 4 months calculated as percentage of plaque and necrotic plaque area of aortic tissue. Data shown represent mean ± SEM. a P < 0.05 vs. control; b P < 0.05 vs. orchiectomy; c P < 0.05 vs. leuprolide. (B) Representative images of H&E-stained sections. The width of the lesions is indicated. Magnification ×600. Bar = 100 μm. H&E = hematoxylin and eosin. (Color version of figure is available online.)

So,
in subjects without pre established atherosclerosis (CVD)
ADT induces risk factors for CVD (over and above those that are associated with PC) and thus atherosclerosis

- Adiposity and dysfunctional fat
- Dysglycemia
- Dyslipidemia
- Hypertension

Mode specific extent:
Orchiectomy >= GnRH agonists > GnRH antagonists
But,

in subjects with established atherosclerosis (CVD) ...

ADT induced plaque instability hence CVS events
Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

Sean O’Farrell, Hans Garmo, Lars Holmberg, Jan Adolfsson, Pär Stattin, and Mieke Van Hemelrijck

Fig 2. Hazard ratios at selected time intervals since the start of androgen-deprivation therapy for first cardiovascular disease (CVD) event in men with differing baseline CVD over duration of (A) gonadotropin-releasing hormone (GnRH) agonist, (B) antiandrogen (AA) therapy, and (C) surgical orchectomy versus the comparison cohort.
Plaque rupture
ADT induced (de-novo) atherosclerosis

Fig. 8. (A) Aortic atherosclerotic plaque area in LDLR<sup>−/−</sup> mice receiving different modes of ADT (n = 9–13/group) at 4 months calculated as percentage of plaque and necrotic plaque area of aortic tissue. Data shown represent mean ± SEM. <sup>a</sup> P < 0.05 vs. control; <sup>b</sup> P < 0.05 vs. orchiectomy; <sup;c</sup> P < 0.05 vs. leuprolide. (B) Representative images of H&E-stained sections. The width of the lesions is indicated. Magnification ×600. Bar = 100 μm. H&E = hematoxylin and eosin. (Color version of figure is available online.)

GnRH-receptor agonists induce necrosis in pre-established atherosclerotic plaques.

Untreated

Degarelix

Leuprolide

Anki Knutsson et al EAU meeting 2015 Abstract #558
Among men with prior CVD, the 1-year event risk with GnRH antagonist was reduced compared with GnRH agonist.
**Effects of ADT on macrophage plasticity in atherosclerosis**

**M1 macrophages**
- Classically activated
- Pro-inflammatory, pro-atherogenic
- Cause tissue injury and promote lesion development as well as enhance plaque vulnerability

**M2 macrophages**
- Alternatively activated
- Anti-inflammatory, athero-protective
  - M2a: involved in tissue repair and can stabilize vulnerable plaques
  - M2b and M2c: regulatory and anti-inflammatory and stabilize or even regress atherosclerotic plaques

**Mannose Receptor (anti-inflammatory M2 macrophages)**

**Mac3-IHC of atherosclerotic plaque in hearts of ADT mice**

Leuprolide

Degarelix

MR-positive area (% of total plaque):
- Leuprolide: 0.005
- Degarelix: 0.01
Foam cells play a significant role in plaque progression and instability.
Atherosclerotic Plaque

- **GnRH agonist**
- **GnRH antagonist**
- **RANK**
- **Monocyte**
- **Increased RANK**
- **Th1 Cell**
- **Secrete RANKL**
- **IFN-γ**
- **TNFα**

- **Macrophage**
- **Reduced collagen synthesis**
- **Collagenases**
- **Plaque Instability**
- **Rupture**
- **Thromboembolic Event**

**Lumen**

- **Platelets**
- **Platelet Activation**
- **Clot fragmentation**
ApoE-/-:Ins2+/Akita Mouse Model of Accelerated Atherosclerosis

Venegas-Pino et al 2015 (in press)
Survival of Ins2+/Akita:apoE-/- mice

Plaque Free  < 50% Occluded  > 50% Occluded  100% Occluded

A B C D

ApoE+/RD  ApoE-/Ins2+/Akita RD  ApoE+/WD  ApoE-/Ins2+/Akita WD

Survival (%)

survival (%)

0 25 50 75 100

0 5 10 15 20 25 30 35 40
time (weeks)

Control
Leuprolide
Degarelix

Survival of Ins2+/Akita:apoE-/- mice
Take home massages (#2)

- ADT induce obesity, metabolic syndrome and atherosclerosis (CVD) to a mode specific extent.

- FSH levels may have a role in this effect.

- In patients with pre-existing atherosclerosis ADT may induce plaque instability (changes in macrophage plasticity?, calcium deposition and tear? plaque hemorrhage?)

- Opportunity for selection of more “cardio-friendly” ADT?
**Role of Androgen Deprivation Therapy In Cardiovascular Disease – A Longitudinal Prostate Cancer**

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Institution</th>
<th>Project Title</th>
<th>Funded Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jehonathan Pinthus</td>
<td>McMaster University</td>
<td>Role of androgen deprivation therapy in cardiovascular disease - a longitudinal prostate cancer study (RADICAL PC)</td>
<td>$3,449,136</td>
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The Role of Androgen Deprivation Therapy in Cardiovascular Disease – A Longitudinal Prostate Cancer Study (RADICAL PC1) - prospective cohort study

A Randomized Intervention for Cardiovascular And Lifestyle Risk Factors in Prostate Cancer Patients (RADICAL PC2) – prospective randomized controlled (prevention) trial
Key Epidemiologic Observations

• Men with PC are at high risk of CVD
• The role of ADT in promoting CVD remains uncertain
Unanswered Questions

• What are the most important determinants of CVD in men with PC?
• How can we prevent CVD in men with PC?
New prostate cancer (diagnosed within 1 year) or commencing ADT for the 1st time
N=6000

RADICAL PC1
Observational registry
N=1884

Intervention:
Systematic CV risk factor management
N=2058

RADICAL PC2
Randomized, controlled trial
N=4116

Control:
Usual care
N=2058

Clinical outcomes (N=6000) at average 3 years’ follow-up
RADICAL PC1 - Objectives

• To determine in a representative, contemporary sample of men with PC (and in particular men treated with ADT):
  a) the prevalence of CVD risk factors and disease, and
  b) the incidence of adverse CVD events

• To evaluate the relationship of ADT with adverse CVD events

• To identify factors (clinical factors and PC treatments) that are independently associated with the development of CVD in men with PC, and in particular in men treated with ADT
RADICAL PC2 - Objectives

Primary
To determine whether a systematic CV and lifestyle risk factor modification strategy reduces the risk of CVD in men with a new diagnosis of PC or who are commencing ADT.

Secondary
In men with a new diagnosis of PC or who are commencing ADT:
• To determine whether a systematic CV and lifestyle risk factor modification strategy improves the CV risk profile
• To estimate the incremental cost-effectiveness ratio of a systematic CV and lifestyle risk factor modification strategy
Inclusion Criteria

PC that is either:

• New (i.e. the diagnosis was made within 1 year), or

• Treated with ADT for the first time within 1 month prior to the baseline visit, or

• To be treated with ADT for the first time within 1 month after the baseline visit
Exclusion Criteria

• Unwilling to provide consent, or
• <45 years of age

Patients will be eligible for RADICAL PC1, but will not be eligible for RADICAL PC2 if:
1) they see a cardiologist every year; or
2) if they are undertaking all of:
   – aspirin use
   – statin use
   – ACE-I or ARB use
   – exercise ≥4 times per week
Intervention in RADICAL PC2

- Randomized in an open manner to usual care or
- Systematic risk factor management
  - Aspirin
  - Statin
  - ACE-I for BP >130/80
  - ARB
  - Dietary counseling
  - Exercise advice
  - Support to quit smoking
# RADICAL PC Procedures

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<tr>
<th>Study procedure</th>
<th>Baseline visit</th>
<th>3-month phone</th>
<th>6-month phone</th>
<th>12-month visit</th>
<th>18-month phone</th>
<th>24-month visit</th>
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<th>Close-out visit</th>
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<td>Vital signs</td>
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<td>X</td>
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Outcomes

Co-primary efficacy outcomes:

• Composite of cardiovascular death, myocardial infarction, stroke, heart failure, or arterial revascularization

• Composite of cardiovascular death, myocardial infarction, stroke, or heart failure
Power Calculation

RADICAL PC1
N=6000 has 90% power to detect hazard ratio as large as 0.86, assuming 30% primary outcome event rate and 5% loss-to-follow-up

RADICAL PC2
N=4116, experiencing 434 primary outcome events will have 85% power to detect hazard ratio of 0.75 in intervention group, assuming 30% drop-in, 15% drop-out, 5% loss-to-follow-up
Specimen Processing

Allow to clot at room temperature for ~30 minutes

Transfer serum from tube evenly into each of 8 cryovials (~1.0 mL ea.)

Carefully draw EDTA plasma off cells & transfer into 1 cryovial

Transfer 1.8 ml of urine to each vial (4)

Transfer 1.8 ml of whole blood into each vial (2)

Centrifuge

Transfer respun plasma from evenly into each of 2 cryovials (~1.0 mL ea.)

R&D

Coagulation

Buffy coat, Genetics

Cryovials should be placed in the freezer boxes provided and frozen within 2 hours of collection, if possible. Collection tubes are discarded after completion of processing.
Mega bio-bank

Blood

Urine

DNA

R&D

Hormonal markers (FSH, Estrogen)

CVS markers (HSTP, Pro-BNP)

Renal markers (Cystatin C)

Metabolic markers (adipokines, inflammatory markers)

Coagulation markers
VISION Study

- 15,133 patients undergoing non-cardiac surgery
- Troponin measured 6-12 hours, 1, 2, and 3 days post-op

Significance of Findings

• First prospective cohort study of PC/ADT with defined CVD end points
• Potential discovery of risk stratification methods
• Large bio-bank
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